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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte PETER DROGE, NICOLE CHRIST, and ELKE LORBACH

Appeal 2010-003660
Application 10/082,772
Technology Center 1600

Before DONALD E. ADAMS, LORA M. GREEN, and
STEPHEN WALSH, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's rejection of claims 29, 30, 32-39, 43-51, and 58. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claim 29 is representative of the claims on appeal, and reads as follows:

> 29. A method of sequence specific recombination of DNA in a eukaryotic cell, comprising:
>
> (a) providing said eukaryotic cell, said cell comprising a first DNA segment integrated into the genome of said cell, said first DNA segment comprising an *attB* sequence according to SEQ ID NO: 1 or a derivative thereof, an *attP* sequence according to SEQ ID NO:2 or a derivative thereof, an *attL* sequence according to SEQ ID NO:3 or a derivative thereof, or an *attR* sequence according to SEQ ID NO:4 or a derivative thereof;
>
> (b) introducing a second DNA segment into said cell, wherein if said first DNA segment comprises an *attB* sequence according to SEQ ID NO: 1 or a derivative thereof, said second DNA segment comprises an *attP* sequence according to SEQ ID NO:2 or a derivative thereof, wherein if said first DNA segment comprises an *attP* sequence according to SEQ ID NO:2 or a derivative thereof, said second DNA segment comprises an *attB* sequence according to SEQ ID NO: 1 or a derivative thereof, wherein if said first DNA segment comprises an *attL* sequence according to SEQ ID NO:3 or a derivative thereof said second DNA segment comprises an *attR* sequence according to SEQ ID NO:4 or a derivative thereof, or wherein if said first DNA segment comprises an *attR* sequence according to SEQ ID NO:4 or a derivative thereof said second DNA segment comprises an *attL* sequence according to SEQ ID NO:3 or a derivative thereof; and
>
> (c) further comprising providing to said cell a modified bacteriophage *lambda* integrase Int, wherein said modified Int is Int-h or Int-h/218, which induces sequence specific recombination through said *attB* and *attP* or *attR* and *attL* sequences.

The following grounds of rejection are before us for review:

I. Claims 29, 30, 32, 33, 36, 38, 44-48, and 58 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Crouzet[1] and Christ & Dröge.[2]

II. Claims 29 and 43 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Crouzet and Christ & Dröge, as further combined with Capecchi.[3]

III. Claims 29, 34, 35, 36, 37, and 39 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Crouzet and Christ & Dröge, as further combined with Hartley.[4]

IV. Claims 29 and 49-51 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Crouzet, Calos,[5] Hartley and Christ & Dröge.

We affirm.

ISSUE

Has the Examiner established by a preponderance of the evidence that the combination of Crouzet and Christ & Dröge renders the method of claim 29 prima facie obvious?

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[1] Crouzet et al., US 6,143,530, issued Nov. 7, 2000.
[2] Nicole Christ and Peter Dröge, *Alterations in the Directionality λ of Site-specific Recombination Catalyzed by Mutant Integrases in Vivo*, 288 J. MOL. BIOL. 825-836 (1998).
[3] Capecchi et al., US 5,464,764, issued Nov. 7, 1995.
[4] Hartley et al., US 5,888,732, issued Mar. 30, 1999.
[5] Calos, US 6,632,672 B2, Oct. 14, 2003.

FINDINGS OF FACT

FF1. The Examiner's statement of Rejection I may be found at pages 5-7 of the Examiner's Answer.[6] As Appellants do not argue the claims separately, we focus our analysis on claim 29, and claims 30, 32, 33, 36, 38, 44-48, and 58 stand or fall with that claim.

FF2. We adopt the Examiner's findings of fact as our own. We also reiterate the following findings.

FF3. The Examiner also relies on Lange-Gustafson[7] as evidence that the ordinary artisan would reasonably expect the mutant integrase INT-h to function at some level in eukaryotic cells (Ans. 18-20).

FF4. Specifically, Lange-Gustafson teaches

> In contrast to the wild-type *int* gene product (Int^+), which produces almost no recombinants in the absence of IHF, purified Int-h protein sponsors reduced but significant levels of integrative recombination in the absence of any *E. coli* supplement. This shows that the *int* gene encodes all the information necessary for the elementary steps in recombination and implies that IHF functions as an accessory protein.

(Lange-Gustafson, Abstract.)

FF5. The reference further teaches:

> Int-h uses supercoiled DNA more effectively than nonsupercoiled DNA as a substrate for recombination, as does Int^+. However, in the absence of IHF, Int-h recombines

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[6] All references to the Examiner's Answer are to the Answer dated December 24, 2008.

[7] Brenda J. Lange-Gustafson and Howard A. Nash, *Purification and Properties of Int-h, a Variant Protein Involved in Site-specific Recombination of Bacteriophage λ*, 259 J. BIOL. CHEM. 12724-12732 (1984).

> supercoiled and nonsupercoiled substrates identically, indicating that IHF is an important part of the mechanism that senses the supercoiled state of the substrate DNA during recombination.

(*Id.*)

FF6. The Dröge Declaration states:

> [O]ne has to realize that DNA substrates (whether episomal or genomic) are negatively supercoiled inside *E. coli.* It was, therefore, not obvious to one of ordinary skill to deduce from the existing data that the mutant recombinase would work inside mammalian cells where the DNA is topologically relaxed. In fact, up to this day, the reason why both Int-h and the double mutant Int-h/218 are functional in eukaryotic cells remains a mystery. One possibility is that there is an unidentified mammalian co-factor which supports the prokaryotic recombinase. Based on these facts, a claim that the invention is "obvious" reflects a thorough misunderstanding of the topic.

(Dröge Declaration, ¶3.)

PRINCIPLES OF LAW

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability" *Id.* at 417. In determining whether obviousness is established by combining the teachings of the prior art, "the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). In addition, a

reference disclosure is not limited only to its preferred embodiments, but is available for all that it discloses and suggests to one of ordinary skill in the art. *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976). Moreover, all that is required is a reasonable expectation of success, not absolute predictability of success. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

ANALYSIS

Appellants argue that Crouzet "worked with wild-type integrases in eukaryotic cells, while Christ & Dröge worked in prokaryotic systems with mutant integrases" (App. Br. 3). Appellants assert that the requirements for prokaryotic cells as used by Christ & Dröge cannot be extrapolated to eukaryotic cells (*id.* at 6). Thus, according to Appellants, there is no reasonable expectation that the mutant integrase of Christ & Dröge would work in the system of Crouzet, even if their ordinary artisan would have been motivated to combine the two references, which deal with two very distinct systems (*id.* at 3).

Appellants assert further that the Examiner has dismissed the Declaration of Dr. Dröge submitted under 37 C.F. R. § 1.132 (*id.* at 6). Appellants argue that the Declaration states that "the skilled artisan could not predict the success of using modified integrases in eukaryotic cells for the simple reason that it is well known that the organization of the prokaryotic genome is distinct from eukaryotics" (*id.*). According to Appellants: "***Without the aid of topogically underwound DNA, which exists only in prokaryotic cells, it was reasonable to assume that mutant Int proteins cannot function***" (*id.* at 7).

Appellants' arguments are not convincing. As acknowledged by Appellants in their arguments, Crouzet worked with wild-type integrases, such as lambda integrase, in eukaryotic system. Christ & Dröge teaches mutants of that integrase, Int-h and Int-h/218. Thus, we agree with the Examiner that as the wild-type integrase works in eukaryotic cells, the ordinary artisan would have had a reasonable expectation of success that the mutant integrases would also function at some level in eukaryotic cells.

Moreover, as taught by Lange-Gustafson, Int-h may use non-supercoiled DNA as a substrate (*see* FF5). Thus, Lange-Gustafson is evidence that rebuts the Dröge Declaration. In addition, given that Crouzet is evidence that the ordinary artisan would have expected the wild-type integrase to work in eukaryotic cells, the Declaration does not explain why the ordinary artisan would not expect the mutant integrases to work in view of Crouzet, which teaches the use of the wild-type enzyme in eukaryotic cells.

As to Lange-Gustafson, Appellants argue that the work in that reference was performed *in vitro*, and thus has "'***nothing*** to do with the environment inside a living eukaryotic cell'" (App. Br. 5-6). Appellants also assert that Crouzet had not shown the functionality of Lambda integrase in eukaryotics, and the reference's "inclusion of any and all type of cell host, ***especially*** mammalian animal cells, was prophetic and completely unsupported from a scientific standpoint" (Reply Br. 5). Thus, Appellants assert, "it cannot be argued that Crouzet [ ] supports or suggests the use of eukaryotic cells" (*id.*).

Appellants' argument as to Crouzet appears to be counter to their arguments in the main brief on Appeal, where they state that Crouzet "worked with wild-type integrases in eukaryotic cells" (App. Br. 3). Moreover, "[i]n patent prosecution, the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to unclaimed disclosures) in that patent that are at issue." *Amgen, Inc. v. Hoescht Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003 (footnote and citation omitted). Thus, "a presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled," which Appellants "can then overcome [ ] by proving that the relevant disclosures of the prior art patent are not enabled." *Id.* Here, Appellants have presented no evidence that the Crouzet reference is not enabling, and arguments of counsel cannot take the place of evidence in the record. *In re Scarbrough*, 500 F.2d 560, 566 (CCPA 1974). As to Lange-Gustafson, Appellants again have not provided any evidence that the ordinary artisan would expect the mutant enzyme to function completely differently in the eukaryotic cell than *in vitro*. Moreover, as already discussed, Crouzet provides the reasonable expectation that the mutants would function in eukaryotic cells by teaching the use of the wild type enzyme in eukaryotic cells.

As to the remaining rejection, Appellants argue that the additionally cited references do not remedy the deficiencies of the combination of Crouzet and Christ & Dröge (App. Br. 8-9; *see also* Reply Br. 3). Those arguments are not found to be convincing for the reasons set forth above.

CONCLUSION OF LAW

We conclude that the Examiner has established by a preponderance of the evidence that the combination of Crouzet and Christ & Dröge renders the method of claim 29 prima facie obvious. As claims 30, 32, 33, 36, 38, 44-48, and 58 stand of fall with that claim, we affirm the rejection of claims 29, 30, 32, 33, 36, 38, 44-48, and 58 under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Crouzet and Christ & Dröge.

As Appellants only argue that the additionally applied references do not remedy the deficiencies of the combination of Crouzet and Christ & Dröge, we also affirm rejections II, III, and IV, the remaining rejections on appeal.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

LMG

SW

DEA

cdc